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Docking, pharmacophore modeling, virtual screening, and selection of test compounds

TK Teresa Kaserer DS Daniela Schuster

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An abbreviated version of this protocol was published in eLIFE in Dec 2019

Modulating FOXO3 transcriptional activity by small, DBD-binding molecules

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Detailed protocol

Docking

- Download the pdb file of the entry 2UZK [1] from the Protein Data Bank [2] (http://www.rcsb.org)
- Open the Wizard in GOLD version 3.1 [3]
- Delete the nucleic acid chains B, D, E, and F in the GOLD/Hermes visualizer
- Wizard step 1 – Select one or more proteins: Click “Load Protein” in the Wizard Pop-up window and select the 2uzk.pdb file
- Wizard step 2 – Protein setup: Click onto the “2UZK” Tab next to “Global Options”
- Add Hydrogens and delete all waters
- Wizard step 3 – Define the binding site: Select an atom of His212 in chain A to define the binding site
- Select all atoms within 20 Å
- Wizard step 4 – Optional: Load a configuration template: leave as is
- Wizard step 5 – Select ligands: Click Add and select the ligand file containing the molecules you want to dock
- Wizard step 6 – Choose a fitness function: select the GoldScore as scoring function
- Wizard step 7 – Genetic Algorithm search options: select Slow (most accurate). Please note, if you want to dock a large library of compounds, you may want to consider using one of the other options
- Wizard step 8 – Finish basic GOLD configuration: Click “Advanced”
- Go to “Output Options” and select the output folder. Save solutions to one file and as sd-file.
- Click “Run GOLD”

Pharmacophore modelling and virtual screening

- Open LigandScout 3.0 [4]
- Create an .ldb file containing up to 250 conformers of the molecules in your screening library (e.g. sd-file downloaded from SPECS (www.specs.net) or Maybridge (www.maybridge.com) and prepped). Please note, depending on the size of your screening library and the flexibility of the compounds, you may want to adjust the number of conformers to be calculated
- Load the pharmacophore models into the Screening Tab
- Define the models you want to use for screening
- Click Advanced option and set max. number of omitted features to zero, tick “Check exclusion volumes” box
- Load the database of calculated conformers
- Click the “Perform Screening” button
- Save the list of virtual hits as sd-file

Please note: Depending on the software version, input structures, etc. you may retrieve differing results. We would therefore strongly advise to validate the pharmacophore models and check, whether your newly generated S9 structure does still match His212_Arg211_model1.pmz.

Selection of test compounds

- Dock the virtual hit list retrieved by pharmacophore modelling using the Docking parameters described above
- Load the 2uzk pdb file into LigandScout
- Select chains B and E
- Select “Move Selection to Ligand Side” in the “Molecule” Tab
- Click on yellow box around chains B and E to zoom into binding site
- Load docking poses of pharmacophore hits into protein by clicking “Insert…” in the “File” tab.
- Automatically generate pharmacophore model and receptor surface for visual inspection of docking poses and to aid selection of test compounds

References:

[1] Tsai KL, Sun YJ, Huang CY, Yang JY, Hung MC, Hsiao CD. Crystal structure of the human FOXO3a-DBD/DNA complex suggests the effects of post-translational modification. Nucleic Acids Res. 2007;35(20):6984-94. DOI:10.1093/nar/gkm703

[2] Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE. The Protein Data Bank. Nucleic Acids Res. 2000 Jan 1;28(1):235-42. DOI:10.1093/nar/28.1.235

[3] Jones G, Willett P, Glen RC, Leach AR, Taylor R. Development and validation of a genetic algorithm for flexible docking. J Mol Biol. 1997 Apr 4;267(3):727-48. DOI:10.1006/jmbi.1996.0897

[4] Wolber G, Langer T. LigandScout: 3-D pharmacophores derived from protein-bound ligands and their use as virtual screening filters. J Chem Inf Model. 2005 Jan-Feb;45(1):160-9. DOI:10.1021/ci049885e

Related files

FOXO3_pharmacophore_models.zip

How to cite:(Readers should cite both the Bio-protocol preprint and the original research article where this protocol was used)

1. Kaserer, T. and Schuster, D. (2020). Docking, pharmacophore modeling, virtual screening, and selection of test compounds. Bio-protocol Preprint.

bio-protocol.org/prep268.

2. Hagenbuchner, J., Obsilova, V., Kaserer, T., Kaiser, N., Rass, B., Psenakova, K., Docekal, V., Alblova, M., Kohoutova, K., Schuster, D., Aneichyk, T., Vesely, J., Obexer, P., Obsil, T. and Ausserlechner, M. J.(2019). Modulating FOXO3 transcriptional activity by small, DBD-binding molecules. eLIFE. DOI: 10.7554/eLife.48876